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Economic burden of HPV9-related diseases: a real world cost analysis from Italy

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Introduction

Human papillomavirus (HPV) is the most common sexually transmitted virus and causes a substantial burden of disease in both men and women [1]. The prevalence of HPV remains unacceptably high. In 2013-2014, approximately 45 percent of men and 40 percent of women between the ages of 18 and 59 had genital HPV infection [2]. Genital HPV infections are contracted through unprotected vaginal or anal sexual intercourse and skin-to-skin genital contact. HPV infections that result in oral or upper respiratory malignancies are mostly contracted through unprotected oral sex [3]. Most HPV infections are asymptomatic and resolve within a few months of exposure. However, the infection can progress to form pre-cancerous and cancerous lesions. HPV has been shown to be the cause of several clinically significant conditions. As of this writing, more than 100 types of papillomavirus strains that can infect humans have been identified. These have been divided into high- and low-risk types according to their risk of progressing to cancer. The high-risk oncogenic variants of HPV, specifically genotypes 16 and 18, account for approximately 70% of all cases of invasive cervical cancer and cervical dysplasia worldwide [4, 5]. They also account for a smaller fraction of cancers of the vulva, vagina, anus, penis, head and neck [6]. The low-risk HPV variants of genotypes 6 and 11 are responsible for approximately 90% of benign external anogenital warts [7] and almost all cases of recurrent respiratory papillomatosis (RRP) [8, 9].

Primary prevention of HPV-related diseases is possible with vaccination. Three vaccines (Cervarix, Gardasil and Gardasil9) are currently approved for the prevention of HPV infection. All of these vaccines are active against the high-risk HPV 16 and 18 strains, while Gardasil® also protects against HPV 6 and 11. Gardasil9 was authorized in the European market in 2015 and protects against nine strains of HPV, including types 6, 11, 16, 18, 31, 33, 45, 52 and 58 [10, 11]. The availability of these

vaccines has led to the initiation of population-wide immunization programmes in most western countries. Based on previous cost-effectiveness studies, the primary aim of most HPV immunization programmes has been to protect women against cervical cancer [12-14]. However, a study published in 2012 demonstrated the relevance of the burden of HPV malignancies in men to all who pay for healthcare services (the Italian National Health System, NHS) [15]. A subsequent study demonstrated the cost-effectiveness of gender-neutral immunization in Italy [14]. Based on these findings, in 2017, the Italian Government became the first of the G9 countries to introduce a universal, recommended and free vaccination for HPV for girls and boys at the age of 12 [16].

Because of these policy changes, the aim of the study was to provide an estimate of the total, direct medical costs attributable to HPV infection, with stratification of the burden by sex as well as specific diseases using cost inputs taken from the Italian National Health Service. Furthermore, this study also calculated an aggregate measure of the total economic burden attributable to HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58 infections as an estimate of the potential savings due to the introduction of the nine-valent universal HPV vaccination programme.

Methods

Study design:

The study design was developed using the Italian National Health Service (NHS), from which the cost inputs were selected. A systematic review of the literature was conducted to identify economic and epidemiological data related to each HPV-induced disease. The review was aimed to identify the best secondary data available to produce lifetime costs per case estimates. In particular we searched for epidemiological data such as incidence and prevalence rates as well as direct cost estimates from the perspective of the Italian national payer. As a result, lifetime costs for cervical dysplasia, anogenital warts and cervical cancer were modelled based on a number of previously published studies (Table 1) [17]. Due to the lack of available information regarding RRP in the Italian context, treatment assumptions were speculated for this disease on the basis of international literature as well as tariffs applied by Italian diagnosis-related groups (DRGs).

Real-world data were used to estimate hospital-based management costs of the main HPV-induced malignancies: cervical, vulvar, vaginal, penile, head and neck cancer. Specifically, hospital discharge records (HDRs) from 2010 to 2014 from the administrative archives of the Marche region were analysed to identify hospitalization rates as well as the costs associated with HPV-related diseases. This approach was followed and validated by previous publications made in this field [[18]]. Finally, outpatient costs related to these malignancies were estimated based on the latest national tariffs (2013) for specialist consultation procedures, and treatment paradigms were validated by the expert opinions of a group of clinicians. An incidence-based approach was then adopted to estimate lifetime costs per case and produce an aggregate measure of the economic burden. The relative prevalence rates of HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58 according to the literature were applied to estimate the aggregate fraction of costs attributable to HPV infections in Italy.

Real-world data analysis:

Information related to the hospital discharges (HDRs) of all accredited public and private hospitals in the Marche Region, both for ordinary and day-care regimens, were included to estimate the costs of cervical, vulvar, vaginal, penile, head and neck cancer. The total costs related to hospitalizations were calculated using the DRGs (with 2013 values) of hospitalized patients based on their age, gender and their consumption of resources during their hospital stay. The DRG system aggregates all activities, including surgical interventions, administered drugs, expended materials and

personnel for each individual diagnosis and stipulates the reimbursement tariff. This value corresponds to the total amount of all interventions provided that is to be paid to the hospital. According to the DRG-based reimbursement system, every hospitalized patient was assigned to a group of diagnostically homogeneous cases; therefore, patients with the same DRG values were assigned the same reimbursement charges.

We included hospitalizations of patients who were residents of the Marche region, were older than 18 years of age, and who presented one of the following codes from the *International Classification of Diseases, 9th revision–Clinical Modification (ICD-9-CM)* as the primary or secondary diagnosis: 'Anal cancers' (154.2–154.8); 'Oropharyngeal cancers' (146.0-146.9); 'Other female genital organs' (184.0-184.9); and 'Penile cancer' (187.1-187.9). A cohort of 810 patients (40% male and 60% female) who were hospitalized in 2010 or 2011 was selected from those who did not fall into any of the reported ICD9-CM diagnosis categories and who had not had other malignant tumours in the two years prior to their first hospital admission (naïve). Subjects were included and then followed for three years after their first hospital admission. Based on expert opinions and [15], we assumed that a three-year period was appropriate in terms of resource utilization to estimate lifetime costs. In addition, outpatient visits were modelled based on the clinical pathway followed by [19] which was validated here by the clinical experts involved in the study. In particular based on the clinical guidelines and current practices, a number of procedures per each diagnose was established to represent the amount of outpatient services provided to patients lifetime. Outpatient costs were then applied based on the 2013 national tariffs for specialists' office consultations and procedures [[15].

Literature review:

Secondary data were identified through a systematic literature review. The search was carried out according to the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) guidelines [20] (Figure 1). The search was conducted in October 2017 and covered the period of 1990 to 2017. The analysis was performed through the online MEDLINE (Medical Literature Analysis and Retrieval System) bibliographic archive of MEDLARS using the PubMed search system and EMBASE accessed through OVID SP. To retrieve robust data that were relevant to Italy, the inquiry was integrated with grey literature obtained from generic academic search engines (e.g., Google Scholar) and websites such as the Italian Ministry of Health, the Italian National Institute of Health

(NIH), and those of Italian scientific societies such as the Italian Society of Health Technology Assessment (SIHTA). The search keys used to conduct the literature are reported in Annex B.

Screening and data extraction:

Two independent researchers screened the titles and abstracts. Full-text articles were included if they met the following inclusion criteria: 1) they reported epidemiological data (incident cases by disease and the prevalence of HPV by genotype) derived from population databases, such as national surveys or registries; and 2) they reported direct cost data from the perspective of the payer and expressed monetary values for hospital DRGs and outpatient tariffs. Studies were also required to contain estimates of reported lifetime costs or appropriate data to estimate these costs. For all phases of the literature review, disagreements were resolved by discussions among the entire team to reach a consensus.

Figure 1: Literature review, PRISMA

Lifetime costs:

An incidence-based approach was adopted in which the lifetime costs per case associated with each condition were applied to the estimated number of incident cases that were attributable to HPV. We sought to develop cost-per-case estimates that represented the current values of the total direct medical costs accrued from the time of diagnosis to the end of follow-up (Table 1).

Specifically, cost estimates for cervical cancer were obtained from a published Italian study [17] that estimated the mean total direct costs for cervical cancer, including those generated by the management of disease progression and recurrence. The actual costs were not reported, although the median follow-up duration of the cohort was 23 months (range 1–89). We assumed that the mean cost per patient for primary tumour treatment (€13,122) was incurred within year 1, whereas the mean cost associated with the management of disease progression and recurrence (€9,092) was incurred in the following year, and we reduced this second-year value by 3% (€8,827). The selected discount rate (3%) reflects the opportunity costs of financing from the perspective of a public payer (the Italian NHS) according to Italian AIES (Italian Health Economics Association) guidelines [21].

Lifetime costs associated with the clinical and surgical management of cervical dysplasia were estimated from published Italian data [22, 23].

The lifetime cost per patient of non-cervical malignancies was modelled on the national treatment guidelines of a previously published study [15]. Therefore, in addition to the real-world data used

to estimate the lifetime costs of hospitalization, we also included two clinical examinations conducted by specialists and two two-sector computed tomography (CT) scans per year. These costs were then reported over a 3-year follow-up period, which is consistent with the real-world data according to [15] and expert opinion. Outpatient fees were attributed to each surgical procedure and medical treatment using national outpatient tariff values (2013). Hospitalization costs (including outpatient costs) incurred after the first 12 months of treatment were discounted at a rate of 3% per year to obtain their current net value expressed in the value of the Euro in 2013.

The estimated lifetime cost of anogenital warts per incident case was calculated as the sum of the mean, inflation-adjusted direct costs incurred by new patients (€416 for women and €311 for men) and the probable, discounted, inflation-adjusted mean direct costs of recurrent (€199 for women and €66 for men) and resistant (€48 for women and €92 for men) episodes observed over one year after initial diagnosis. These figures were modelled on a previously published article [24]. Probability rates were calculated based on the number of recurrent (50.6% for women and 34.8% for men) and resistant (28.2% for women and 38.5% for men) cases reported as a percentage of the annual number of newly diagnosed cases, assuming a steady state in the total number of genital warts treated in Italy [24].

Finally, to estimate the lifetime cost per RRP patient, elective surgical procedures and medical treatments were selected according to published reports from the US [25, 26]. Treatment assumptions included the management of complicated respiratory infections, three acute clinical treatments, 4.4 surgical procedures, and a tracheotomy rate of 11% per year [25]. Italian DRG tariffs for 2013 were applied to the selected procedures. The duration of the disease was estimated to be 4.2 years [25]. All costs incurred after the first 12 months of treatment were discounted at a rate of 3% per year to obtain their current net value expressed in the value of the Euro in 2013.

All costs related to each HPV-induced disease included in the study (Table 1) were adjusted for inflation in 2018 using the compound annual Italian National Consumer Price Indexes (NIC) provided by the Italian National Institute of Statistics (ISTAT).

Table 1: Estimates of lifetime cost per patient by diagnosis

Diagnoses	***Surgical procedures and medical treatments***	***Direct cost per procedure or medical treatment***	***Compound inflation rate ^***	***Lifetime direct cost per incident patient (2018 Euro)***	***Source***
		a	*b*	*a x b*	
Cervical cancer					

	Management of primary tumour	€13,122	117.50%	€ 15,418	[17]
	Discounted cost of progression/recurrence after 1 year	€8,827	117.50%	€ 10,372	[17]
	Lifetime cost per patient	€21,949		€ 25,790	
Cervical dysplasia					
	Abnormal PAP smears	€25	117.50%	€ 29	[22]
	Colposcopies	€101	117.50%	€ 119	[22]
	Diagnosis of cervical dysplasia	€34	117.50%	€ 40	[23]
	CIN1 treatment	€686	117.50%	€ 806	[27]
	CIN2 treatment	€1,242	117.50%	€ 1,459	[27]
	CIN3 treatment	€1,763	117.50%	€ 2,072	[27]
	Lifetime cost per patient	€4,011		€ 4,525	
Anal cancer (Women)					
	Tot, lifetime hospitalizations	€9,607	109.30%	€ 10,500	ICD9-CM (154.2-154.3;154.8)
	Follow-up 2 clinical examinations (x3)	€20.66	102.20%	€ 42	Outpatient tariff (89.7) [19]
	Follow-up sector CT scan (x3)	€74.88	102.20%	€ 77	Outpatient tariff (87.03) [19]
	Follow-up sector CT scan (x3)	€77.67	102.20%	€ 79	Outpatient tariff (87.41) [19]
	Follow-up sector CT scan (x3)	€79.47	102.20%	€ 81	Outpatient tariff (88.01) [19]
	Lifetime cost per patient	€9,860	3%	€ 11,570	
Anal cancer (Men)					
	Tot, lifetime hospitalizations	€15,876	109.30%	€ 17,353	ICD9-CM (154.2-154.3;154.8)
	Follow-up 2 clinical examinations (x3)	€20.66	102.20%	€ 42	Outpatient tariff (89.7) [19]
	Follow-up sector CT scan (x3)	€74.88	102.20%	€ 77	Outpatient tariff (87.03) [19]
	Follow-up sector CT scan (x3)	€77.67	102.20%	€ 79	Outpatient tariff (87.41) [19]
	Follow-up sector CT scan (x3)	€79.47	102.20%	€ 81	Outpatient tariff (88.01) [19]
	Lifetime cost per patient	€16,129	3%	€ 18,422	
Oropharyngeal cancer (Women)					
	Tot, lifetime hospitalizations	€11,210	109.30%	€ 12,253	ICD9-CM (146.0-146.9) [19]
	Follow-up 2 clinical examinations (x3)	€20.66	102.20%	€ 42	Outpatient tariff (89.7) [19]
	Follow-up sector CT scan (x3)	€77.67	102.20%	€ 79	Outpatient tariff (87.41) [19]
	Follow-up sector CT scan (x3)	€79.47	102.20%	€ 81	Outpatient tariff (88.01) [19]
	Lifetime cost per patient	€11,388	3%	€ 13,029	
Oropharyngeal cancer (Men)					
	Tot, lifetime hospitalizations	€23,096	109.30%	€ 25,244	ICD9-CM (146.0-146.9)
	Follow-up 2 clinical examinations (x3)	€20.66	102.20%	€ 42	Outpatient tariff (89.7) [19]
	Follow-up sector CT scan (x3)	€77.67	102.20%	€ 79	Outpatient tariff (87.41) [19]
	Follow-up sector CT scan (x3)	€79.47	102.20%	€ 81	Outpatient tariff (88.01) [19]
	Lifetime cost per patient	€23,274	3%	€ 26,021	
Vulvar and vaginal cancer					
	Tot, lifetime hospitalizations	€11,084	109.30%	€ 12,115	ICD9-CM (184.0-184.4;184.8-184.9)
	Follow-up 2 clinical examinations (x3)	€20.66	102.20%	€ 42	Outpatient tariff (89.26) [19]

	Follow-up sector CT scan (x3)	€77.67	102.20%	€ 79	Outpatient tariff (87.41) [19]
	Follow-up sector CT scan (x3)	€79.47	102.20%	€ 81	Outpatient tariff (88.01) [19]
	Lifetime cost per patient	€11,262	3%	€ 12,890	
Penile cancer					
	Tot, lifetime hospitalizations	€7,031	109.30%	€ 7,685	ICD9-CM (187.1-187.9)
	Follow-up 2 clinical examinations (x3)	€20.66	102.20%	€ 42	Outpatient tariff (89.7) [19]
	Follow-up sector CT scan (x3)	€77.67	102.20%	€ 79	Outpatient tariff (87.41) [19]
	Follow-up sector CT scan (x3)	€79.47	102.20%	€ 81	Outpatient tariff (88.01) [19]
	Lifetime cost per patient	€7,209	3%	€ 8,461	
Anogenital warts (Women)					
	Direct outpatient costs for new patients	€368	119.80%	€ 441	[24]
	Discounted cost of recurrence after 1 year (50.6% prob)	€176	119.80%	€ 211	[24]
	Discounted cost of resistance after 1 year (28.2% prob)	€43	119.80%	€ 52	[24]
	Lifetime cost per patient	€587		€ 703	
Anogenital warts (Men)					
	Direct outpatient costs for new patients	€275	119.80%	€ 329	[24]
	Discounted cost of recurrence after 1 year (34.8% prob)	€59	119.80%	€ 71	[24]
	Discounted cost of resistance after 1 year (38.5% prob)	€82	119.80%	€ 98	[24]
	Lifetime cost per patient	€416		€ 498	
RRP					
	Management of complicated throat infection	€5,744	102.20%	€ 5,870	DRG 79
	Acute clinical treatment of throat infection (x3)	€9,650	102.20%	€ 29,587	DRG 76
	Minor throat surgery (x4.4)	€4,378	102.20%	€ 19,687	DRG 63
	Tracheostomy (11% rate)	€8,737	102.20%	€ 982	DRG 75
	Annual cost per patient	€28,509		€ 56,126	
	Lifetime cost per patient		3%	€ 224,860	

^Costs have been adjusted for 2018 inflation values using the compound annual Italian National Consumer Price Indexes [28] from 2005 (119.8%), 2006 (117.5%), 2010 (109.3%), and 2013 (102.2%).

Legend: cervical intra-epithelial neoplasia (CIN), recurrent respiratory papillomatosis (RRP), computed tomography (CT), total (Tot), prob (probability).

Incidence and HPV9 genotype attribution:

An estimate of the incident cases in the population over 18 years of age in Italy in 2018 [29] was obtained from the systematic literature review using the mean of the ranges provided by the selected studies (Table 3). Crude incident rates per 100,000 residents in the 2018 resident Italian population [29] were calculated (Table 2). Due to the heterogeneity of the rates reviewed and the number of diseases involved, no standardization, meta-analyses or adjustments for the pyramidal stratification of the observed population were attempted. Due to a lack of Italian epidemiological

data, the incidence of RPP was deliberately selected from the lower limit of the range cited in the literature [15].

Moreover, to estimate the costs attributable to HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58, prevalence rates of HPV DNA and genotype attribution per condition were identified from the systematic review. Specifically, for each condition, we first calculated the percentage of DNA attribution to exclude all cases that were not a result of HPV infection. We then applied prevalence rates from the literature to calculate the individual fractions attributable to genotypes included in HPV9 vaccine (Table 2 and Annexe A). These values were used to calculate the fraction of the total economic burden of HPV-induced malignancies attributable to the nine genotypes by both disease and sex according to the number of estimated incident cases.

Table 2: Incidence rates, the prevalence of HPV, and HPV9 genotype fractions

Diagnoses	*Incidence rates (per 100,000)*	*HPV DNA+ (%)*	*HPV9 fraction*	*Source*
Cervical cancer	4.5	100.0%	89,4%	[30-32]
Abnormal PAP smears	699.2	100.0%	91,5%	[15]
Colposcopies	195.4	100.0%	94,0%	[15]
Diagnosis of cervical dysplasia	657.1	100.0%	35,0%	[15]
CIN1 treatment	35.9	100.0%	75,0%	[15, 32, 33]
CIN2 treatment	9.1	100.0%	72,5%	[15, 32, 33]
CIN3 treatment	10.0	100.0%	57,2%	[15]
Anal cancer	1.7	88.0%	89.8%	[30, 34]
Oropharyngeal cancer	15.5	40.0%	73.7%	[35, 36]
Vulvar and vaginal cancer	2.3	36.6%	86.4%	[31]
Penile cancer	0.8	50.0%	81.6%	[30, 37]
Anogenital warts	241.6	100.0%	90.0%	[15, 34]
RRP	0.4	100.0%	95.0%	[38-40]

Legend: cervical intra-epithelial neoplasia (CIN), recurrent respiratory papillomatosis (RRP).

Statistical analyses:

Probabilistic and Deterministic Sensitivity Analyses (PSA and DSA) were developed to account for the variability of data used in the model. The PSA employed the differences found in the examined sources indicating minimum and maximum values of the uncertainty distribution for each parameter. The probabilistic distribution was prepared by applying normally reported values for the development of probabilistic models in economic evaluations, distinguishing between costs (gamma distribution) and epidemiological parameters (beta distribution) [41]. The distribution of each

parameter was then used to perform 5,000 Monte Carlo simulations to obtain interval estimates (95% Confidence Interval (CI)) for the main epidemiological and economic data (Annex C).

The DSA was performed by adjusting each parameter to the highest and lowest possible values of the data obtained from the systematic review with a one-way approach. When a plausible range was not available from the literature, we assumed a variation of 10%.

The critical parameters used to assess the uncertainty were: the number of incident cases per year, the HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58, genotype attributions and cost parameters. We measured the impact of inserting the highest and lowest values for: (a) all diseases, (b) only oncologic diseases (defined as the sum of cervical, anal, oropharyngeal, vulvar, vaginal and penile cancers) (c) non-oncologic (cervical dysplasia, anogenital warts and RRP).

Cost estimates of innovative therapeutic options not included in the DRG tariffs:

The DRG tariffs used as the main inputs for evaluating the direct costs of hospitalization did not include the costs of innovative therapeutic options that were added to the treatment guidelines for HPV-induced malignancies after 2013. The costs of these new drugs were actually debited to a National Account (named "File F"), which was specifically created to account for highly innovative therapeutic options. However, the administrative costs were paid for by the DRG tariff. File F is not accessible and does not provide information on the use of innovative drugs by indication. Therefore, identifying the resources allocated from File F used to treat HPV-induced malignancies is impossible. Ignoring these costs, however, would significantly underestimate the burden of HPV-induced diseases carried by the NHS. Therefore, we used the scenario analysis [42] method to estimate a range of credible costs for the innovative therapies used to treat HPV-induced malignancies. Following the latest guidelines of the Associazione Italiana di Oncologia Medica (AIOM) for the treatment of HPV-induced malignancies, two innovative therapeutic options were identified:

- Cetuximab (Erbitux), indicated for the treatment of head and neck cancer;
- Bevacizumab (Avastin), indicated for the treatment of recurrent or refractory cervical cancer.

The treatment and cost inputs used to determine the three scenarios are reported in Annex A.

Results

The annual incidence of the nine HPV-related conditions corresponded to approximately 1.1 million cases of which 975 thousand associated to cervical conditions (86%), and 158 thousand to non-cervical (14%). In 2018, the total direct costs (expressed relative to the 2018 Euro) associated with the annual incident cases of cervical cancer, cervical dysplasia, vulvar, vaginal, anus, penis and head and neck cancers, anogenital warts, and RRP in Italy were estimated to be €542.7 million, with a credible range of €346.7 - €782.0 million. These costs could increase considering also the impact of innovative therapies for cancers treatment included in the scenario analysis with a plausible range between €16.2 and €37.5 million. The fraction attributable to the nine HPV9 genotypes included in our base case analysis, without considering the impact of innovative therapies, was €329.5 million (range €157.0 - €564.9 million), accounting for approximately 61% of the total annual burden of HPV-related diseases in Italy.

Cervical conditions:

The total cost estimate for cervical conditions was €149.9 million (range €132.0 - €168.9 million), which corresponds to 28% of the total economic burden associated with HPV-related diseases in Italy, (Table 5). Of this amount, €69.7 (range €59.1 - €81.2 million) and €80.2 million (range €66.2 - €95.6 million) were due to cervical cancer and total cervical dysplasia, respectively – estimates that include diagnosis, colposcopies, PAP smears and cervical neoplasia (CIN1/2/3). Additionally, the total annual cost associated with the management of cervical lesions, including the diagnosis and treatment of CIN1/2/3 stages, was €54.0 million (range €41.0 - €68.7 million).

The fraction of cervical conditions attributable to HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58 was estimated to be €118.3 million (range €104.2 - €133.3 million), 53% of which was related to cervical cancers (€62.3 million, range €52.6 - €72.8).

Non-cervical malignancies:

We evaluated the direct costs related to the treatment and follow-up of HPV-related cases of seven non-cervical malignancies: cancer of the anus, oropharynx, vulva, vagina, and penis, anogenital warts and RPP. The economic burden associated with non-cervical conditions was €392.9 million, with a range of €206.3 to €638.4 million. The amount corresponds to 72% of the total costs associated with HPV-related diseases in Italy. Oropharyngeal cancers were responsible for the highest annual burden of direct costs (€215.7 million, €187.0 for men and €28.7 for women),

followed by anogenital warts (€85.9 million, €41.2 for men and €44.6 for women) and RPP (€53.6 million). The costs related to all HPV-related diseases included in our study are reported in Table 5. According to our systematic review, HPV virus were responsible for 36.6% of vulvar and vaginal cancers and 40% of oropharyngeal cancers, respectively, as well as 88% and 50% [30] of anal and penile cancers, respectively. The estimated fractions of the total annual direct costs attributable to HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58-induced non-cervical malignancies were €211.2 million (range €58.5 - €460.1 million), 61% of which was attributable to HPV 6 and 11.

Cost of innovative therapies not included in DRG tariffs.

Table 4 reports the outcomes of the scenario analysis. Three scenarios were obtained by varying the potential number of patients treated and the future availability of similar treatments at a reduced price. The credible range of the incremental costs allocated to innovative treatments of HPV-induced malignancies was €16.2 - €37.5 million. This range represents a significant incremental cost compared to the DRG tariffs for the HPV-induced malignancies, ranging from 12.8% to 29.8%. The availability of similar therapies would reduce the incremental cost by approximately 22%.

Table 3: Total lifetime costs and HPV-9 attributable fraction

	Diagnoses	***Estimated number of incident cases per year***	***Total lifetime direct costs per disease (mill Euro)***	***HPV9 attributable costs (mill Euro)***
a	Cervical cancer	2,698	€ 69.7	€ 62.3
	(CI 95%)	*(2,502-2,902)*	*(€59.1-€81.2)*	*(€52.6-€72.8)*
b	Abnormal PAP smears	422,922	€ 12.3	€ 11.2
	(CI 95%)	*(345,068-507,585)*	*(€9.1-€15.8)*	*(€7.8-€15.1)*
c	Colposcopies	118,214	€ 14.0	€ 13.1
	(CI 95%)	*(95,649-142,480)*	*(€10.3-€18.2)*	*(€9.1-€17.8)*
d	Diagnosis of cervical dysplasia	397,444	€ 15.9	€ 5.6
	(CI 95%)	(321,588-480,112)	*(€11.7-€20.6)*	*(€3.8-€7.6)*
e	CIN1 treatment	21,715	€ 17.5	€ 13.1
	(CI 95%)	(17,706-26,141)	*(€13-€22.6)*	*(€9.3-€17.6)*
f	CIN2 treatment	5,532	€ 8.0	€ 5.8
	(CI 95%)	(1,998-10,735)	*(€2.8-€16)*	*(€1.9-€11.8)*
g	CIN3 treatment	6,047	€ 12.6	€ 7.2
	(CI 95%)	(2,290-11,646)	*(€4.5-€24.6)*	*(€2.5-€14.4)*
h	Total cervical lesions *(d + e + f + g)*	430,738	€ 54.0	€ 31.7
	(CI 95%)	(35,4125-513,625)	*(€41-€68.7)*	*(€23.3-€41.3)*
i	Total cervical dysplasia *(b + c + h)*	971,874	€ 80.2	€ 56.0
	(CI 95%)	(857,453-1,090,683)	*(€66.2-€95.6)*	*(€46-€67.1)*
l	**Total cervical conditions *(a + i)***	**974,572**	**€ 149.9**	**€ 118.3**
	(CI 95%)	**(860,140-1,093,375)**	***(€132-€168.9)***	***(€104.2-€133.3)***
m	Anal cancer (women)	620	€ 7.2	€ 5.7
	(CI 95%)	(528-720)	*(€5.6-€8.9)*	*(€4.3-€7.3)*
n	Anal cancer (men)	437	€ 8.0	€ 6.4
	(CI 95%)	(360-522)	*(€6.1-€10.3)*	*(€4.6-€8.4)*
o	Oropharyngeal cancer (women)	2,200	€ 28.7	€ 8.4

	(CI 95%)	(2,168-2,232)	*(€23.6-€34.3)*	*(€6.4-€10.8)*
p	Oropharyngeal cancer (men)	7,200	€ 187.0	€ 55.1
	(CI 95%)	(7,184-7,216)	*(€153.3-€224.1)*	*(€41.2-€70.9)*
q	Vulvar and vaginal cancer	1,418	€ 18.3	€ 5.8
	(CI 95%)	(1,275-1,566)	*(€14.6-€22.3)*	*(€4.4-€7.3)*
r	Penile cancer	494	€ 4.2	€ 1.7
	(CI 95%)	(411-582)	*(€3.2-€5.3)*	*(€1.3-€2.2)*
s	Anogenital warts (women)	63,447	€ 44.6	€ 40.1
	(CI 95%)	(51,697-76,430)	*(€34.5-€56)*	*(€28.5-€53.6)*
t	Anogenital warts (men)	82,674	€ 41.2	€ 37.1
	(CI 95%)	(67,432-99,496)	*(€32.1-€51.5)*	*(€26.4-€49.5)*
u	RRP	249	€ 53.6	€ 51.0
	(CI 95%)	(0-1,660)	*(€0-€372.8)*	*(€0-€356)*
v	***Total non-cervical conditions (m + n + o + p + q + r + s + t + u)***	**158,739**	**€ 392.9**	**€ 211.2**
	(CI 95%)	**(139,079-179,749)**	***(€206.3-€638.4)***	***(€58.5-€460.1)***
z	**Total burden *(l + v)***	**1,133,312**	**€ 542.7**	**€ 329.5**
	(CI 95%)	**(1,016,911-1,253,343)**	***(€346.7-€782)***	***(€157-€564.9)***

Legend: cervical intra-epithelial neoplasia (CIN), recurrent respiratory papillomatosis (RRP).

Table 4: Credible range of incremental direct costs of the innovative therapies not included in DRG tariffs

	Base case: (HPV9 burden)	Scenario 1: CRT H&N + bevacizumab recurrent CC	Scenario 2: CRT + CCT in H&N + bevacizumab for recurrent & metastatic CC	Scenario 3: =Scenario 2 but biosimilars available (25% off)	Source
Base case - Oropharyngeal cancer					
Incident patients infected by HPV9-susceptible strains	2,771	2,771	2,771	2,771	
Cost/patient	€ 22,980	€ 22,980	€ 22,980	€ 22,980	
Total cost (Euro mill)	€ 63.7	€ 63.7	€ 63.7	€ 63.7	
Incremental Cetuximab scenarios					
Cetuximab + RT in patients >70 years (28% of total eligible)		776	776	776	
Incremental cost of Cetuximab added to RT/patient		€ 8,133	€ 8,133	€ 6,133	[43]
Total incremental cost (Euro mill)		€ 6.3	€ 6.3	€ 4.8	
Cetuximab + CT in Stage III-IV patients in good performance condition (80%)			€ 443.4	€ 443.4	
Incremental cost of Cetuximab added to CT/patient			€ 5,201.0	€ 3,907.3	[43]
Total incremental cost (Euro mill)			€ 2.3	€ 1.7	
Base Case - Cervical Cancer					
Incident patients infected by HPV9-susceptible strains	2,412	2,412	2,412	2,412	
Treatment cost/patient	€ 25,790	€ 25,790	€ 25,790	€ 25,790	
Total cost (Euro mill)	€ 62	€ 62	€ 62	€ 62	
Incremental Bevacizumab scenarios					
Incident cervical patients HPV9+ and VEGF+ (60% of incident)		€ 1,447	€ 1,447	€ 1,447	[44]
Recurrent patients (31% of incident VEGF+)		€ 449	€ 449	€ 449	[45]
Incremental cost of Bevacizumab added to CT		€ 21,966	€ 21,966	€ 16,475	
Total incremental cost (Euro mill)		€ 10	€ 10	€ 7	
Metastatic patients (60% of incident VEGF+)			€ 868	€ 868	[45]
Incremental cost of Bevacizumab added to CT			€ 21,966	€ 16,475	[46]
Total incremental cost (Euro mill)			€ 19.07	€ 14.31	
TOTAL TREATMENT COST PER SCENARIO (Euro mill)	€ 125.9	€ 142.1	€ 163.4	€ 154.1	
INCREMENTAL COST vs BASE CASE (Euro mill)		€ 16.2	€ 37.5	€ 28.2	
Incremental cost as a % of Base case					

Legend: oropharyngeal cancer (OPC), cetuximab (C), radiation therapy (RT), chemotherapy (CT), vascular endothelial growth factor (VEGF), cervical cancer (CC).

The fraction of HPV9-genotype costs attributable to men was equal to €137.7, while women accounted for €194.4. This corresponded to 58% of total costs attributable to HPV9 infections for women, whereas men accounted for 42%. On the other hand, the economic burden of HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58 infections that were related to non-cervical conditions was higher for men than women (64.4% vs 35.6% of the total, respectively), (Figure 2).

Figure 2: Fractions of HPV 9 costs by gender

Legend: recurrent respiratory papillomatosis (RRP).

The Tornado chart shown in Figure 3 shows that the uncertainty in our evaluation of the economic burden of HPV9-related diseases is mostly associated with the range of possible incidence rates for all groups of disease and costs.

Figure 3: Deterministic Sensitivity Analysis (DSA)

Legend: Oncologic: cervical, anal, oropharyngeal, vulvar, vaginal and penile cancers

Discussion

The purpose of this analysis was to estimate the economic burden of HPV-related diseases in Italy. Our study attempted to measure the direct costs from the real world data perspective of the Italian National Health Service. The authors adopted a real-world data approach to estimate lifetime costs and conducted a systematic literature review to construct our estimation models with the most recent data available. Additionally, we included the nine HPV genotypes included in the new nine-valent vaccine that was made available in Europe in the last two years. Therefore, the present study is a first attempt to measure the economic burden of HPV-related diseases in Italy considering the newly available vaccine and data. By estimating the resource consumption attributable to the nine genotypes, we aim to predict the effects of both the 2017-2019 National Immunization Plan and the strategies recently adopted in Italy and to inform future public health decisions.

According to the results of this study, costs related to CIN1 treatment, vaginal cancer and cervical cancer were the most heavily influenced when including five HPV genotypes that accounted for 28% of their total cost on average. Furthermore, the economic burden among men represented more than one-third (42%) of the total direct costs of HPV9 genotype-related diseases, including cervical conditions, which is consistent with previously published data [6, 15] and with the effort to extend the anti-HPV immunization programme to include boys in the National Immunization Plan 2017-19.

The present study has several limitations. First, real-world data from administrative archives were only available for anal, head and neck, vulvar, vaginal and penile cancers, and published Italian sources of cost data were limited. Additionally, the quality of the available information was variable. Therefore, the use of different data sources may have diminished the comprehensiveness of our data. Specifically, the use of administrative data required certain assumptions to consistently estimate the lifetime costs from different data sources. Hospital discharge forms may have codification problems; therefore some information may be missing and/or be wrongly reported. In this case, our analysis may have missed this information (due to the inclusion criteria), with the risk of underestimating the economic and epidemiological burden of the considered HPV-related diseases. Additionally, not all diseases led to hospitalization and this may be a further source of underestimation. Additionally, due to the scarcity of available data, we did not include drug utilization in our estimates. These limitations should be considered in future research; however, in our opinion, they do not undermine the validity of the cost estimates in the present study or their estimated impact on the total economic burden of HPV-related diseases. Future research should

address these gaps in epidemiological and cost data to reduce the uncertainty associated with the present estimates. In conclusion, the present analysis is the first to provide a snapshot of the current state of resource utilization in Italy and the expected economic effects resulting from the 2017-2019 National Immunization Plan. Therefore, we believe that this analysis may provide a tool for keeping records of the expected economic effects over time.

References:

1. Goldstone, S., et al., *Prevalence of and risk factors for human papillomavirus (HPV) infection among HIV-seronegative men who have sex with men.* J Infect Dis, 2011. **203**(1): p. 66-74.
2. CDC. *Prevalence of HPV in Adults Aged 18–69: United States, 2011–2014*.
3. Favato, G., et al., *A novel method to value real options in health care: the case of a multicohort human papillomavirus vaccination strategy.* Clin Ther, 2013. **35**(7): p. 904-14.
4. Clifford, G.M., et al., *Human papillomavirus types in invasive cervical cancer worldwide: a meta-analysis.* Br J Cancer, 2003. **88**(1): p. 63-73.
5. Walboomers, J.M., et al., *Human papillomavirus is a necessary cause of invasive cervical cancer worldwide.* J Pathol, 1999. **189**(1): p. 12-9.
6. Chaturvedi, A.K., *Beyond cervical cancer: burden of other HPV-related cancers among men and women.* J Adolesc Health, 2010. **46**(4 Suppl): p. S20-6.
7. Koutsky, L.A., D.A. Galloway, and K.K. Holmes, *Epidemiology of genital human papillomavirus infection.* Epidemiol Rev, 1988. **10**: p. 122-63.
8. Armstrong, L.R., C.S. Derkay, and W.C. Reeves, *Initial results from the national registry for juvenile-onset recurrent respiratory papillomatosis. RRP Task Force.* Arch Otolaryngol Head Neck Surg, 1999. **125**(7): p. 743-8.
9. Armstrong, L.R., et al., *Incidence and prevalence of recurrent respiratory papillomatosis among children in Atlanta and Seattle.* Clin Infect Dis, 2000. **31**(1): p. 107-9.
10. Hartwig, S., J.J. Baldauf, and G. Dominiak-Felden, *Estimation of the epidemiological burden of HPV-related cancers, precancerous lesions, and genital warts in women and men in Europe: potential additional benefit of a nine-valent compared to the quadrivalent HPV vaccine*. 2015.
11. *FDA approves Gardasil 9 for prevention of certain cancers caused by five additional types of HPV*. 2014 12/11/2014 12 Aug 2015]; Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm426485.htm.
12. Jit, M., Y.H. Choi, and W.J. Edmunds, *Economic evaluation of human papillomavirus vaccination in the United Kingdom.* BMJ, 2008. **337**: p. a769.
13. Kim, J.J. and S.J. Goldie, *Health and economic implications of HPV vaccination in the United States.* N Engl J Med, 2008. **359**(8): p. 821-32.
14. Favato, G., et al., *Novel health economic evaluation of a vaccination strategy to prevent HPV-related diseases: the BEST study.* Med Care, 2012. **50**(12): p. 1076-85.
15. Baio, G., et al., *Economic burden of human papillomavirus-related diseases in Italy.* PLoS One, 2012. **7**(11): p. e49699.
16. Salute, M.d., *Piano Nazionale Prevenzione Vaccinale*. 2016.
17. Ferrandina, G., et al., *Hospital costs incurred by the Italian National Health Service for invasive cervical cancer.* Gynecol Oncol, 2010. **119**(2): p. 243-9.
18. Mennini, F.S., et al., *Burden of Disease of Human Papillomavirus (HPV): Hospitalizations in the Marche and Veneto Regions. An observational study.* Clin Drug Investig, 2018. **38**(2): p. 173-180.
19. Ministero della Salute, *Remunerazione prestazioni di assistenza ospedaliera per acuti, assistenza ospedaliera di raibilitazione e di lungodegenza post acuzie e di assistenza specialistica ambulatoriale.* 2013, Pubblicato sulla GURI N. 23 del 28/01/2013 Suppl. n. 8.
20. Moher, D., et al., *Preferred reporting items for systematic reviews and meta-analyses: the*

PRISMA statement. PLoS Med, 2009. **6**(7): p. e1000097.
21. Fattore, G., *Proposta di linee guida per la valutazione economica degli interventi sanitari in Italia.* PharmacoEconomics Italian Research Articles, 2009. **11**(2): p. 83-93.
22. Mennini, F.S., et al., *Anti-HPV vaccination: a review of recent economic data for Italy.* Vaccine, 2009. **27 Suppl 1**: p. A54-61.
23. Giorgi Rossi, P., et al., *Epidemiology and costs of cervical cancer screening and cervical dysplasia in Italy.* BMC Public Health, 2009. **9**: p. 71.
24. Merito, M., et al., *Treatment patterns and associated costs for genital warts in Italy.* Curr Med Res Opin, 2008. **24**(11): p. 3175-83.
25. Bishai, D., H. Kashima, and K. Shah, *The cost of juvenile-onset recurrent respiratory papillomatosis.* Arch Otolaryngol Head Neck Surg, 2000. **126**(8): p. 935-9.
26. Hu, D. and S. Goldie, *The economic burden of noncervical human papillomavirus disease in the United States.* Am J Obstet Gynecol, 2008. **198**(5): p. 500 e1-7.
27. Mennini, F.S., et al., *Health and economic impact associated with a quadrivalent HPV vaccine in Italy.* Gynecol Oncol, 2009. **112**(2): p. 370-6.
28. Istat. 2017; Available from: https://rivaluta.istat.it.
29. Istituto Nazionale di Statistica (ISTAT). *Popolazione residente al 1 Gennaio 2017*. Statistiche Demografiche 2017; Available from: http://demo.istat.it/.
30. AIOM, A., *I numeri del cancro in Italia 2017*, I.P.S. Editore, Editor. 2017.
31. Serrano, B., et al., *Human papillomavirus genotype attribution for HPVs 6, 11, 16, 18, 31, 33, 45, 52 and 58 in female anogenital lesions.* Eur J Cancer, 2015. **51**(13): p. 1732-41.
32. WHO, I., Information Centre on HPV and CervicalCancer (HPV Information Centre). *Human Papillomavirus and Related Cancers in Italy*, I. Summary Report, Editor. 2017.
33. Garcia-Espinosa, B., E. Moro-Rodriguez, and E. Alvarez-Fernandez, *Genotype distribution of human papillomavirus (HPV) in histological sections of cervical intraepithelial neoplasia and invasive cervical carcinoma in Madrid, Spain.* BMC Cancer, 2012. **12**: p. 533.
34. Hartwig, S., et al., *Estimation of the epidemiological burden of human papillomavirus-related cancers and non-malignant diseases in men in Europe: a review.* BMC Cancer, 2012. **12**: p. 30.
35. Abogunrin, S., et al., *Prevalence of human papillomavirus in head and neck cancers in European populations: a meta-analysis.* BMC Cancer, 2014. **14**: p. 968.
36. Castellsague, X., et al., *HPV Involvement in Head and Neck Cancers: Comprehensive Assessment of Biomarkers in 3680 Patients.* J Natl Cancer Inst, 2016. **108**(6): p. djv403.
37. Miralles-Guri, C., et al., *HPV prevalence and type distribution in penile carcinoma.* Journal of clinical pathology 2009.
38. Donne, A.J., et al., *The role of HPV type in Recurrent Respiratory Papillomatosis.* Int J Pediatr Otorhinolaryngol, 2010. **74**(1): p. 7-14.
39. Fusconi, M., et al., *Recurrent respiratory papillomatosis by HPV: review of the literature and update on the use of cidofovir.* Acta Otorhinolaryngol Ital, 2014. **34**(6): p. 375-81.
40. Lacey, C.J., C.M. Lowndes, and K.V. Shah, *Chapter 4: Burden and management of non-cancerous HPV-related conditions: HPV-6/11 disease.* Vaccine, 2006. **24 Suppl 3**: p. S3/35-41.
41. Briggs, A.H., K. Claxton, and M.J. Sculpher, *Decision modelling for health economic evaluation*. Handbooks in health economic evaluation series. 2006, Oxford: Oxford University Press. x, 237 : ill. ; 24 cm.
42. Favato G and Vecchiato R, *Embedding real options in scenario planning: A new methodological approach.* Technology Forecasting and Social Change, 2017. **124**(November 2017): p. 135-49.
43. Brown, B., et al., *An economic evaluation of cetuximab combined with radiotherapy for patients with locally advanced head and neck cancer in Belgium, France, Italy,*

Switzerland, and the United Kingdom. Value Health, 2008. **11**(5): p. 791-9.
44. Mandic, A., S. Usaj Knezevic, and T. Kapicl Ivkovic, *Tissue expression of VEGF in cervical intraepithelial neoplasia and cervical cancer.* J BUON, 2014. **19**(4): p. 958-64.
45. Friedlander, M., M. Grogan, and U.S.P.S.T. Force, *Guidelines for the treatment of recurrent and metastatic cervical cancer.* Oncologist, 2002. **7**(4): p. 342-7.
46. Tewari, K.S., et al., *Bevacizumab for advanced cervical cancer: final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240).* Lancet, 2017. **390**(10103): p. 1654-1663.